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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,201	06/27/2005	Michael Mandola	UMD-0097	2039

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
01/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/532,201	MANDOLA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6 and 11* is/are pending in the application.

4a) Of the above claim(s) *1,3 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II in the reply received on 10/15/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1, 3, and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/5/07.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 11 is indefinite because step (b) requires detecting "one or more polymorphisms" in a thymidylate synthase (hereinafter TS) nucleic acid molecule that was obtained from an individual. First, it is not clear how one detects a polymorphism in an individual. A polymorphism is difference in a particular nucleic acid sequence among individuals. Therefore, in a single individual, one could detect the alleles present in a particular nucleic acid molecule, but one could not detect differences among individuals in a single person. After the recitation of physical process steps the claim recites a three part "wherein clause." This clause refers to

particular possible genotypes in an individual, with each of the three parts referring to different genotypes at different positions within the TS nucleic acid. Each of the three portions of the wherein clause refers to different positions or combinations of position within the TS nucleic acid. It is not clear how these wherein recitations relate to the recited process steps- namely does applicant intend that particular positions within the TS gene are required to be assayed? The single "detecting" step of the claim makes no such requirement, yet the "wherein" clause appears to refer to particular positions within the TS gene. There is a disconnect between the clear active process steps which require the detection of one or more unspecified polymorphisms and the "wherein" clauses which refer to alleles at particular polymorphic positions. How do the three different parts of the wherein clause relate to one another and how do they effect the scope of the claim? They do not appear to structurally effect the method steps. There is no conjunction joining the three portions of the clause- are all three portions required to be met in order to practice the claim? How does one know if all three portions are met?

Priority

6. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/420,164, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for one or more claims of this application. The provisional application does not discuss the +6/-6 deletion polymorphism which is referred to in claim 11. Furthermore, the provisional application does not provide enabling support for the claimed invention for at least the same reasons that the instant specification does not provide enabling support for the claimed invention. Therefore, the filing date of the instant claim is the effective filing date of this application: 10/21/03.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 11 is rejected under 35 U.S.C. 102(a) and 102(b) as being anticipated by Ulrich et al. (Cancer Research, June 2002, as cited in the IDS).

Ulrich et al. teach a method which comprises steps of obtaining a nucleic acid sample comprising a thymidylate synthase nucleic acid molecule and detecting the alleles one or more polymorphisms in the thymidylate synthase nucleic acid. Namely, Ulrich et al. detect the alleles present in the so called 28-bp repeat polymorphism and the 3'UTR 6-bp deletion polymorphism, and further teach that the 3R/3R genotype is associated with an increased risk of developing cancer in patients low or medium folate intake (Figure 1 and p.3363 2nd column). Ulrich et al. further teach that the 6-bp deletion is not associated with risk of colorectal adenoma, and

therefore, the association with the 3R/3R genotype would be present with the + or - 6bp alleles. Therefore, the teachings of Ulrich et al. anticipate the claimed invention.

9. Claim 11 is rejected under 35 U.S.C. 102(a) as being anticipated by Mandola et al. (Cancer Research, as cited in the IDS).

Mandola et al. teach a method which comprises obtaining a sample of nucleic acid from an individual and detecting one or more polymorphisms in the TS nucleic acid molecule in the sample. Namely, Mandola et al. detect alleles present of the common repeat polymorphism of the 5' UTR of the TS gene and also of a single nucleotide polymorphism within this gene. Mandola et al. teach that an additional 28 bp repeat within the 5' UTR can enhance transcriptional activation of TS due to the presence of a USF binding site in the repeat, teach that the single nucleotide polymorphism can abolish the ability of USF proteins to bind to this site. Mandola et al. are silent as to the relationship of these polymorphisms to predisposition to cancer or CVD, but they clearly complete the structurally required steps of the instantly claimed method. The relationships set forth in the "wherein" clauses are statements of inherent properties of the presence of the particular alleles.

10. Claim 11 is rejected under 35 U.S.C. 102(a) as being anticipated by Kawakami et al. (Cancer Research, September 2003, as cited in IDS).

Kawakami et al. teach a method which comprises obtaining a sample of nucleic acid from an individual and detecting one or more polymorphisms in the TS nucleic acid molecule in the sample. Namely, Kawakami et al. detect alleles present of the common repeat polymorphism of the 5' UTR of the TS gene and also of a single nucleotide polymorphism within this gene. Kawakami et al. teach that an additional 28 bp repeat within the 5' UTR can enhance

transcriptional activation of TS due to the presence of a USF binding site in the repeat, teach that the single nucleotide polymorphism can abolish the ability of USF proteins to bind to this site. Kawakami et al. are silent as to the relationship of these polymorphisms to predisposition to cancer or CVD, but they clearly complete the structurally required steps of the instantly claimed method. The relationships set forth in the "wherein" clauses are statements of inherent properties of the presence of the particular alleles.

11. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Lenz et al. Proceedings of the American Association for Cancer Research, Volume 43, March 2002, Abstract #3274, as cited in IDS.

12. Lenz et al. teach a method which comprises obtaining a nucleic acid sample comprising a TS nucleic acid molecule and determining the allele present at the site of the 6-bp deletion polymorphism in the 3' UTR of the TS gene. Lenz et al. teach that patients possessing one or two deletion alleles showed a relative risk of 1.4 when compared with patients having no deletion allele. Thus, Lenz et al. teach a method which meets the structural limitations of the claimed invention.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claim is drawn to a method for determining whether an individual has or has a heightened predisposition to cancer or cardiovascular disease. The active process steps recited in the claim include obtaining a nucleic acid comprising a TS nucleic acid molecule and detecting the presence of one or more polymorphisms within the TS nucleic acid molecule. The claims set forth a series of relationships between TS alleles and the presence of or risk for developing cardiovascular disease or cancer. Thus, the nature of the invention requires the knowledge of a reliable association between the presence of particular alleles of the TS gene and the presence of or predisposition to cardiovascular disease or cancer.

The scope of the claim is quite broad. As written the claim encompasses the detection of any possible polymorphism within a TS nucleic acid, although this is unclear because the wherein clause refers to alleles of particular polymorphisms. The claim encompasses detecting that any type of cancer is present and/or that any possible type of cardiovascular disease is present. These two classes of diseases themselves are quite broad, encompassing many different types of diseases of varying causes, symptoms and outcomes. The claim encompasses detecting the presence of the diseases as well as predicting that the diseases might occur.

The specification provides experiments beginning at ¶0058, but the specification does not provide a single experiment wherein alleles of the polymorphisms analyzed relative to populations of individuals with cancer or cardiovascular disease. The specification does not analyze the effect of any polymorphism on the presence of or predisposition to cancer or cardiovascular disease.

In ¶0061 the specification states that there is a G→C SNP in the 2nd repeat of the 3R allele of the TS promoter polymorphism, that the C allele alters the USF consensus binding ability and that the more non-variant 3R alleles present the worse the response to 5-FU based chemotherapy drugs.

Applicants confirmed that there are two single base changes in the last 28 bp repeat of both the 2R and 3R genotypes, and applicant further identified a single nucleotide polymorphism within the second repeat of the 3R allele (see ¶ 0072 and Figure 1). Applicants refer to the newly identified allele of the SNP as the 3RV allele and as the "variant sequence."

Applicants teach that there is a USF E-box consensus element in the first repeat of the 2R genotype and in the first and second repeats of the 3R genotype. The SNP that applicants identified in the second repeat of the 3R genotype alters this element (¶ 0074). The specification teaches that neither unphosphorylated nor phosphorylated forms of USF-1 showed affinity to the variant sequence in vitro (¶ 0081). Applicants used a chromatin immunoprecipitation assay to show that USF-1 and USF-2 bind the TS locus which includes the tandem repeats and the E-box elements (¶0084).

The specification teaches that a 3RV construct displays similar transcriptional activity as a 2R construct which is lower than the activity of the 3R construct (Figure 5B, ¶ 0088).

The specification teaches that the G→C SNP was only observed in the second repeat of 3R genotypes and that the frequency of the C allele among the second repeat of the 3R was 56% among all 3R carriers in a group of non-Hispanic whites (¶0093).

The specification teaches the analysis of response of 40 patients having colorectal cancer to treatment with 5-fluorourocil (5-FU). No significant response was observed when the

genotypes 3R/3R, 2R/3R and 2R/2R were considered. However, reclassifying the patients based on predicted high and low TS expression using the repeat polymorphism and the SNP polymorphism resulted in a significant result with patients having low-expression TS genotypes having an improved response rate relative to patients with high-expression TS genotypes (¶ 0095-¶0098).

Applicants further completed experiments to characterize the effects of the so called -6 bp/1494 deletion polymorphism, and demonstrate that there are no major mRNA instability or translational silencing elements within the TS-3'UTR (¶0103-0109). Applicant further demonstrated that the -6 bp/1494 construct has decreased mRNA stability compared with +6bp constructs, and that the -6 bp allele has an increased rate of mRNA degradation (¶0110-0114). Aplicants found that patients homozygous for the +6bp allele had significantly higher TS mRNA expression in colorectal tumor tissue than individuals homozygous for the -6bp allele (¶0117).

The specification teaches that in relation to cardiovascular disease treatment, clinicians can determine if a subject is at a higher risk for CVD by looking at the number of non-variant alleles, teaching that the levels of folate will likely be lower and homocysteine will likely be higher than in subjects with more 2R and/or 3RV alleles, thus making that individual more susceptible to CVD (¶ 0067).

The conclusions set forth in the instant claims are not based on empirical association studies between genotypes and risk or incidence of any type of cancer or cardiovascular disease. Instead, they are based upon assumptions in view of the potential effect of the polymorphisms on total folate load in patients and the potential effects of those folate loads on disease risk.

However, it is highly unpredictable when or if these assumptions may actually be true or reproducible.

Zhang et al. found that total folate intake is not associated with overall risk of breast cancer, but may be a mitigate risk of breast cancer associated with alcohol consumption. This is relevant since the conclusions set forth in the instant claim are based, in part, about assumptions concerning the effects of folate metabolism on predisposition to or the presence of disease. However, the assumptions about folate metabolism were not robustly established at the time of filing, especially not with regard to all possible types of cancer or cardiovascular disease.

Applicants claim recites that an individual with the 3R/3R construct in the 5' region of the TS gene and a single +6 bp allele in the 3' untranslated region polymorphism has the highest probability of developing cancer or cardiovascular disease. However, the prior art at the time of filing demonstrates that whether or not this is universally true is highly unpredictable. Ulrich et al. found that for patients with the 3R/3R alleles and high folate intake there is a decreased risk of colorectal adenoma (p. 3363, Urlich et al. 2002, as cited in IDS). This is opposite of the assertions set forth in the instant claim which state that the 3R/3R construct confers a heightened predisposition to cancer or cardiovascular disease. Among individuals with the 2R/2R genotype and high folate intake there was an increased risk for colorectal adenoma (p. 3362). Further, Urlich et al. teach that "[t]he finding of a decreased risk associated with lower TS expression in the presence of low-folate intake (Fig. 1) was unexpected (p. 3363)." It is apparent that the allele status of an individual is not sufficient to predict colorectal carcinogenesis. Skibola et al. teach that the TS 3R/3R genotype conferred a greater level of protection against acute lymphocytic leukemia (Blood, 2002, as cited in IDS). The teachings of Skibola et al. also appear to suggest a

relationship which is opposite of those set forth in the claims where the claims suggest that 3R/3R genotype confers increased risk.

Regarding parts (ii) and (iii), Ulrich et al. found that the allele status of the 6bp allele is not predictive of the risk of colorectal adenomas (p. 3363). Urlich et al. state that "[a]lthough one might expect results similar to those for the TSER polymorphism, because of linkage between the two polymorphisms, these findings illustrate that 'imperfect' disequilibrium may result in different associations with disease phenotypes (p. 3363)." Lenz et al. (cited in IDS) found results that appear to be opposite of those suggested in the claim- namely that it is the presence of the deletion allele (the -6 allele) which confers increased risk of the presence of colorectal cancer.

Further, the scope of the instant claims includes the determination of a heightened predisposition to or the presence of any possible type of cancer or cardiovascular disease. There is no example or evidence in the prior art or in the instant specification which suggests that the presence of any particular allele of the TS gene is sufficient to conclude that an individual has cancer or cardiovascular disease. In fact, such a statement, which is encompassed by the recitation in the claims, is contraindicated by the fact that all alleles can be routinely identified in healthy individuals. Even if the polymorphism is associated with developing some cancers, it is highly unpredictable which cancers are related to alleles of the polymorphism and which are not. For example, Tan et al. teach that compared with the normal expression TS genotype, the low expression TS genotype alone was significantly associated with increased risk for esophageal squamous cell carcinoma but not with gastric cardia adenocarcinoma (abstract; Tan et al. Carcinogenesis, Vol. 26, No. 8, pages 1430-1435, 2005). In addition, there is a total absence of

any data which associates TS genotypes with risk for any type of cardiovascular disease. This is also a highly unpredictable venture. Trinh et al. teach that individuals with the 3R/3R repeat alleles have lower plasma folate levels than other TS genotypes, and that TS genotype may be a genetic marker for homocystinemia and cardiovascular disease risk, but they further teach that "the role of plasma homocysteine in cardiovascular disease is not fully understood" and point out that studies aimed at linking the MTHFR C677T polymorphism to disease risk have been inconclusive (MTHFR C677T is also associated with folate levels; Trinh et al. 2002, cited in IDS). In the post filing date art, Gallekink et al. exemplify this high level of unpredictability. They teach that neither the tandem repeat polymorphism nor the six base pair deletion polymorphism in the TS gene is associated with risk for venous thrombosis in a studied population.

The practice of the claimed invention would require extensive experimentation to discover whether or not the relationships set forth in claim 11 are true for any or all cancers or cardiovascular diseases, and what factors mitigate the relationships. Given the high level of unpredictability and the extreme breadth of the claim, experiments would have to be taken to identify new polymorphisms in the TS gene, to characterize these polymorphisms and to determine their relationship to the presence of disease or likelihood of developing disease. Even for the polymorphisms specifically recited in the claim, there is no evidence of record which suggests that the relationships set forth in the "wherein" clause are actually reliable in view of effects observed in actual populations. Again, extensive experimentation would have to be undertaken to establish relationships for each type of cancer and cardiovascular disease, since

there is no established universal relationship between the presence of these diseases and TS alleles.

Thus, having carefully considered all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

January 7, 2008